PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3228PTWO/AG/a	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11024	International filing date *(day/month/year)* 06.10.2003	Priority date *(day/month/year)* 04.10.2002
International Patent Classification (IPC) or both national classification and IPC C12N5/08		
Applicant ABIOGEN PHARMA S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.04.2004	23.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Teyssier, B Telephone No. +31 70 340-2062

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11024

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-21 as originally filed

Claims, Numbers

1-18 filed with telefax on 26.10.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	17, 18
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	17, 18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the opinion

The amended claims are allowable under Article 34(2)(b) PCT.

Re Item V

Reasoned statement under Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 Cesano *et al.*, *Cancer Research* 1996, 56(13), 3021-3029 (1 July 1996), cited in the application

D2 Visonneau *et al.*, *Clinical Cancer Research* 1997, 3(10), 1789-1797 (October 1997), cited in the application

D3 Tuyaerts *et al.*, *Journal of Immunological Methods* 2002, 264(1-2), 135-151 (1 June 2002)

D4 Berger *et al.*, *Journal of Immunological Methods* 2002, 268(2), 131-140 (15 October 2002)
D4 does not belong to the state of the art (Rule 33.1 a) PCT).

D1 (see p. 3022) and D2 (see p. 1730) describe the large scale expansion of TALL-104 cells in T175 flasks; at a density of 10^6 cells/ml in flasks whose useful volume is slightly below 200 ml, this setting does not allow for the expansion of more than $2 \cdot 10^8$ cells per unit and thus requires polling from several flasks (i.e. "heterogenous culture conditions" according to the definitions of the present application) to prepare doses of at least 10^9 cells. The subject-matter of claims 1-16 is thus new over the prior art represented by D1 or D2 (Article 33(2) PCT).

However the TALL cell lines to be expanded by the homogenous culture process of the invention are the same as in the heterogenous culture process of the prior art. Biological properties such as the level of marker expression cannot confer novelty to the cells of claims 17 and 18; with respect to the results presented in Table 9, this Authority observes that >90% expression of CD3, CD8 or CD56, as reported for TALL cells expanded in heterogenous systems, does not exclude ≥95% or ≥98% expression, as claimed for cells expanded in homogenous systems. More generally, a product endoved with a particular degree of purity shall not be regarded a new over the same product in a less pure form, unless it is established that the skilled person could not reach such a high degree of purity by using means of purification known to him. Therefore the subject-matter of claims 17 and 18 is not new over D1 or D2 (Article 33(2) PCT).

The problem of the application is the homogenous expansion of TALL cells in large quantities (at least

10^9 cells). Neither D1, which is regarded as the closest prior art, nor D2 suggest that this could be achieved by scaling up the suspension culture process described in T175 flasks. The solution proposed is to grow the lymphocytic cells in fermentation units for anchorage-dependent cells, such as a Cell Factory™. D3 and D4 describe the large scale expansion of dendritic cells using Cell Factories™; as presented in D4 (see fig. 1 and first paragraph of p. 139), which does not belong to the state of the art, the advantages of this process over the prior art (use of multiple flasks) are the same as those of the present invention. While D3 discloses that dendritic cells, which are also usually grown in suspension culture, can be successfully expanded in Cell Factories™ designed for adhesion-dependent cells, this document neither teaches nor suggests that Cell Factories™ could be used to expand T lymphocytes such as TALL cells. Therefore, the subject-matter of claims 1-16 involves an inventive step (Article 33(3) PCT).

However claim 1 does not meet the requirements of Article 6 PCT in combination with Rule 6.3(a) PCT in that the matter for which protection is sought is not defined in terms of technical features: Claim 1 merely amounts to a statement of the underlying problem and fails to teach the critical feature that a vessel for anchorage-dependent cells shall be used. The features of dependent claims 2 and/or 3 should be incorporated into the independent claim.

The subject-matter of claims 1-18 is industrially applicable (Article 33(4) PCT).